PHARMACOKINETICS AND DRUG DISPOSITION

Different effects of three transporting inhibitors, verapamil, cimetidine, and probenecid, on fexofenadine pharmacokinetics

Objective: **Fexofenadine is a substrate of P-glycoprotein and organic anion transporting polypeptides. The aim of this study was to compare the inhibitory effects of different transporting inhibitors on fexofenadine pharmacokinetics.**

Methods: **Twelve male volunteers took a single oral 120-mg dose of fexofenadine. Thereafter three 6-day courses of either 240 mg verapamil, an inhibitor of P-glycoprotein, 800 mg cimetidine, an inhibitor of organic cation transporters, or 2000 mg probenecid, an inhibitor of organic anion transporting polypeptides, were administered on a daily basis in a randomized fashion with the same dose of fexofenadine on day 6. Plasma and urine concentrations of fexofenadine were monitored up to 48 hours after dosing.**

Results: **Verapamil treatment significantly increased the peak plasma concentration by 2.9-fold (95% confidence interval [CI], 2.4- to 4.0-fold) and the area under the plasma concentration–time curve from time 0 to infinity [AUC(0-∞)] of fexofenadine by 2.5-fold (95% CI, 2.0- to 3.3-fold). No changes in any plasma pharmacokinetic parameters of fexofenadine were found during cimetidine treatment. AUC(0-∞) was slightly but significantly increased during probenecid treatment by 1.5-fold (95% CI, 1.1- to 2.4-fold). Renal clearance of fexofenadine was significantly decreased during cimetidine treatment to 61% (95% CI, 50%-98%) and during probenecid treatment to 27% (95% CI, 20%-58%) but not during verapamil treatment.**

Conclusion: **This study suggests that verapamil increases fexofenadine exposure probably because of an increase in bioavailability through P-glycoprotein inhibition and that probenecid slightly increases the area under the plasma concentration–time curve of fexofenadine as a result of a pronounced reduction in renal clearance. However, it may be difficult to explain these interactions by simple inhibitory mechanisms on target transporters. (Clin Pharmacol Ther 2005;77:17-23.)**

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Recently, it has become increasingly evident that drug transporters have a pivotal role in pharmacokinetics of numerous drugs with therapeutic implications.[1-6] Numerous studies have revealed that targeted expression of drug uptake and efflux transport to specific cell membrane domains allows for the efficient directional movement of many drugs in clinical use.[1-6] Transport by adenosine triphosphate–dependent efflux pumps, such as P-glycoprotein and multidrug resistance–related proteins, influences the intestinal absorption[7,8]

and renal[9,10] or hepatic elimination[11] and central nervous system concentrations[8] of many drugs. Members of the organic anion transporting polypeptides (OATPs) and organic cation transporter (OCT) families of drug uptake transporters have been found to be capable of transporting a large array of structurally divergent drugs.[12-14] OATPs are expressed in the liver, kidney, brain, and intestine and OCTs are expressed in the liver and kidney, suggesting that they may play a critical role in drug interaction, as well as in drug absorption, elimination, and tissue penetration.[15]

Fexofenadine, an active metabolite of terfenadine, is a selective histamine H_1 receptor antagonist and is clinically effective in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria for first-line therapeutic agents like loratadine and cetirizine.[16] In clinical trials fexofenadine did not prolong the QT interval or decrease heart rate, unlike terfenadine, astemizole, and ebastine.[17] Fexofenadine is regarded as a substrate of P-glycoprotein and OATP-A and OATP-B on the basis of several in vitro studies.[18-20] Drug-drug and drug-food interaction reports have shown that rifampin (INN, rifampicin), St John's wort, fruit juice, and verapamil influence alternation of fexofenadine disposition.[21-24] Because fexofenadine is not metabolized, these interactions are explained by modulation of P-glycoprotein and OATPs. However, there are no published data suggesting an in vivo contribution of these transporters to the disposition of fexofenadine.

Verapamil, a short-term inhibitor of mainly P-glycoprotein, has been used to increase the therapeutic effectiveness of cytotoxic anticancer drugs in cancer chemotherapy.[25] More recently, P-glycoprotein reversal agents including verapamil have been demonstrated to alter the pharmacokinetic properties of coadministered agents in therapeutic areas other than oncology.[26] Meanwhile, to identify the renal secretion pathway for a particular drug, in vivo pharmacokinetic drug interaction studies are usually conducted with inhibitors such as cimetidine and probenecid.[27,28] Because cimetidine is known to compete for active tubular secretion primarily with basic drugs,[29] this drug is regarded as an efficient inhibitor of OCT1 and OCT2. In addition, cimetidine has recently been identified as a potent inhibitor of the OATP-C–mediated transport of organic anions.[30] In contrast, probenecid has been known not only as a direct inhibitor of glucuronide conjugation[31] but also as a potent inhibitor of OATPs, because probenecid competitively inhibited the secretion of many weak organic acids.[32,33]

The aim of this study was to compare the inhibitory effects of different transporting inhibitors, verapamil, cimetidine, and probenecid, on fexofenadine disposition. Renal clearance was also examined to clarify the effect of these transporters on excretion of fexofenadine in the kidney. The results suggest that there is an in vivo contribution of these transporters to the disposition of fexofenadine.

METHODS

Subjects. Twelve healthy Japanese male volunteers were enrolled in this study. The mean (±SD) age was 25.2 ± 5.6 years (range, 20-40 years), and the mean body weight was 60.9 ± 6.2 kg (range, 54-80 kg). The Ethics Committee of Hirosaki University School of Medicine, Hirosaki, Japan, approved the study protocol, and written informed consent had been obtained from each participant before any examinations.

Study design. The volunteers took a single oral 120-mg dose of fexofenadine (Allegra; Aventis Pharma Co, Tokyo, Japan) at 9 AM with 240 mL of tap water as a control phase. Thereafter, a randomized crossover study design in 3 treatment phases was conducted at intervals of 2 weeks. Verapamil (two 40-mg tablets) 3 times daily (240 mg/d) (Vasolan; Eisai Pharmaceutical Co, Ltd, Tokyo, Japan), cimetidine (two 200-mg tablets) twice daily (800 mg/d) (Tagamet; Sumitomo Pharmaceutical Co, Ltd, Osaka, Japan), or probenecid (four 250-mg tablets) twice daily (2000 mg/d) (Benecid; Kaken Pharmaceutical Co, Ltd, Tokyo, Japan) with 240 mL of tap water was given for 6 days. Four volunteers within each group were allocated to 1 of 3 different drug sequences as follows: verapamil-cimetidine-probenecid, probenecid-verapamil-cimetidine, or cimetidine-probenecid-verapamil. On day 6, they took a single oral 120-mg dose of fexofenadine with 240 mL of tap water (9 AM) 1 hour after the last 80-mg dose of verapamil, 400-mg dose of cimetidine, or 1000-mg dose of probenecid after overnight fasting (9 AM) with 240 mL of tap water. Treatment medication was not taken after oral administration of fexofenadine. Compliance was confirmed by pill count. No other medications were taken during the study periods. No meal was allowed until 4 hours after dosing (1 PM). No volunteers ingested any fruit juice until at least 8 hours after dosing. The use of alcohol, tea, coffee, and cola was forbidden during the test days.

Sample collections. Blood samplings (10 mL each) for determination of fexofenadine were taken into heparinized tubes just before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hours after the administration of fexofenadine. Urine samples were collected from 0 to 4 hours, 4 to 12 hours, 12 to 24 hours, and 24 to 48 hours after dosing. Plasma was separated immediately and kept at −30°C until analysis. A part of the urine sample

(30 mL) was stored at −30°C until analysis. The remaining urine samples were discarded after the urine volume was recorded.

Assay. Plasma and urine concentrations of fexofenadine were quantitated by use of an HPLC method developed in our laboratory.[34] In brief, 10 μL of 10-μg/mL diphenhydramine (internal standard) diluted with 1 mL of acetate buffer (0.2 mol/L, pH 4.0) was added to samples (1 mL plasma or 0.1 mL urine). Sample purification was performed by solid-phase extraction on C18 minicolumns (BondElut C18, 3 mL, 500 mg packing; Varian, Palo Alto, Calif). The cartridges were preconditioned with 2 mL of methanol, 2 mL of water, and 1.5 mL of acetate buffer (0.2 mol/L, pH 4.0). After sample load, the cartridges were washed with water (2 mL), methanol-water (50:50 [vol/vol]) (2 mL), and methanol (1 mL). After the cartridges were dried, fexofenadine and internal standard were eluted with 50-mmol/L triethylamine in methanol (1 mL). The eluates were dried with airflow, and the residue dissolved in 10 to 300 μL of eluent A was injected into an HPLC system (Shimadzu Class-VP; Shimadzu Co, Kyoto, Japan). The mobile phases were as follows: 0.05-mol/L monobasic potassium phosphate buffer/acetonitrile/methanol (60:35:10 [vol/vol/vol]) (A) and 0.05-mol/L monobasic potassium phosphate buffer/acetonitrile (40:60 [vol/vol]) (B). Chromatographic separation was achieved on an octadecylsilane-80A column (internal diameter, 150 × 4.6 mm; particle size, 5 μm) by use of a linear gradient from A to B in 10 minutes. The peak was detected with a fluorescence detector set at an excitation wavelength of 220 nm and an emission wavelength of 290 nm, and the total time for a chromatographic separation was approximately 17 minutes. The validated quantitation ranges of this method were 1.0 to 500 ng/mL, with coefficients of variation of 0.6% to 9.1%. Mean recoveries were 72.8% to 76.7%, with coefficients of variation of 2.7% to 5.8%. Free fraction was separated from plasma by use of an ultrafiltration technique (Ultracent; Tosou Co, Tokyo, Japan).

Data analyses of pharmacokinetics. The peak concentration (C_{max}) and concentration peak time (t_{max}) were obtained directly from the original data. The terminal elimination rate constant (k_e) was determined by log-linear regression of the final data points (n = 4). The apparent elimination half-life of the log-linear phase ($t_{½}$) was calculated as follows: $t_{½} = 0.693/k_e$. The area under the plasma concentration–time curve (AUC) from 0 to 48 hours [AUC(0-48)] was calculated with use of the linear-linear trapezoidal rule. The AUC from time 0 to infinity [AUC(0-∞)] and elimination half-life were determined by a noncompartmental model with WinNonlin software (Pharsight Corporation, Cary, NC). Residual area was about 0.5% to 6%, and the Console Calculator was used. The amount of drug excreted (A_e) was calculated by volume of urine volume and urine concentration of fexofenadine. Renal clearance was obtained from A_e(0-48)/Free AUC(0-48).

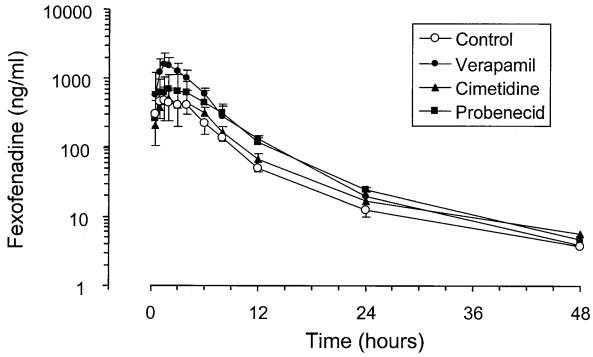

Fig 1. Mean plasma concentration–time curves of fexofenadine after single oral 120-mg dose. *Error bars* indicate SD.

Statistical analyses. Repeated-measures ANOVA was used for comparisons of pharmacokinetic parameters between the control phase and the 3 treatment phases. The comparison of t_{max} was performed by use of the Friedman test. The amount of drug excreted in each sample was compared between the control phase and the 3 treatment phases by use of 2-way ANOVA. A *P* value of .05 or less was regarded as significant. Geometric mean ratios to corresponding values in the control phase with 95% confidence intervals (CIs) were used for detection of significant differences as post hoc analyses. When the 95% CI did not cross 1.0, the result was regarded as significant. SPSS 12.0 for Windows (SPSS Japan Inc, Tokyo, Japan) was used for these statistical analyses.

RESULTS

Although mild side effects were experienced (slight chest pain in 2 cases during verapamil treatment, tendency of diarrhea in 1 case during cimetidine treatment, mild stomach disturbance in 3 cases during probenecid treatment), no clinically significant adverse events were reported throughout the study.

Plasma kinetics. There were significant differences among the 4 treatment groups in pharmacokinetic parameters such as C_{max} ($F = 13.785$; $df = 3,9$; $P = .001$), AUC(0-48) ($F = 10.857$; $df = 3,9$; $P = .002$), and AUC(0-∞) ($F = 10.677$; $df = 3,9$; $P = .003$) (Fig 1). However, no differences were found in t_{max} ($F =$

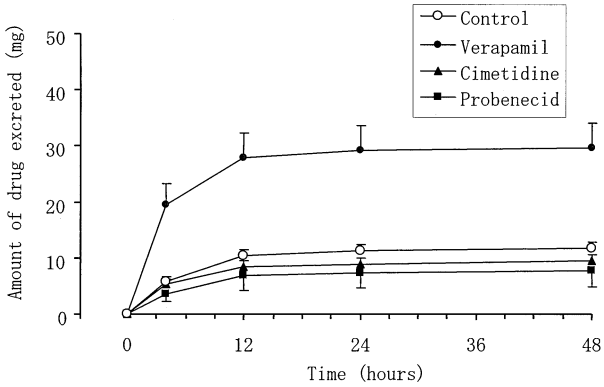

Fig 2. Mean cumulative urinary excretion rate (%) of fexofenadine after single oral 120-mg dose. *Bars* indicate SEs.

1.202; $df = 3,9$; $P = .364$) or elimination half-life ($F = 3.667$; $df = 3,9$; $P = .056$). Post hoc analyses showed that verapamil treatment significantly increased the C_{max} of fexofenadine by 2.9-fold (95% CI, 2.4- to 4.0-fold), the AUC(0-48) of fexofenadine by 2.5-fold (95% CI, 2.0- to 3.4-fold), and the AUC(0-∞) of fexofenadine by 2.5-fold (95% CI, 2.0- to 3.3-fold). In contrast, elimination $t_{½}$ during verapamil treatment was 24% shorter than during the control phase. No changes in plasma pharmacokinetic parameters were found during cimetidine treatment. Probenecid treatment significantly increased the AUC(0-48) of fexofenadine by 1.5-fold (95% CI, 1.1- to 2.5-fold) and the AUC(0-∞) of fexofenadine by 1.5-fold (95% CI, 1.1- to 2.4-fold). All other pharmacokinetic parameters of fexofenadine did not differ during probenecid treatment.

Urinary excretion. There was a significant difference in the amount of drug excretion among the 4 phases (Fig 2). Post hoc analysis showed that verapamil significantly increased the cumulative urinary excretion at 4 hours ($P < .001$), 12 hours ($P < .001$), 24 hours ($P < .001$), and 48 hours ($P < .001$) and the total amount of drug excreted between 0 and 48 hours after administration, whereas the amounts of drug excreted between 0 and 48 hours after administration were significantly decreased during cimetidine treatment by 0.68-fold (95% CI, 0.52- to 0.98-fold) and during probenecid treatment by 0.43-fold (95% CI, 0.27- to 0.97-fold). Renal clearance of fexofenadine was significantly decreased during cimetidine treatment to 61% (95% CI, 50%-98%) and during probenecid treatment to 27% (95% CI, 20%-58%) but not during verapamil treatment (Table I).

DISCUSSION

The results of this study showed a significant increase in plasma concentration of fexofenadine (C_{max} and AUC) during verapamil treatment, without prolonging the elimination half-life of fexofenadine, which is in accordance with previous in vivo and in vitro reports.[19,24] These findings suggest that verapamil increased the bioavailability of fexofenadine but did not inhibit the elimination of fexofenadine, and this might be partially explained by an inhibitory effect of verapamil on P-glycoprotein. Moreover, although the amount of fexofenadine excretion was significantly increased during verapamil treatment, renal clearance was unchanged by verapamil. When the plasma and urine findings are taken together, verapamil increased only the bioavailability of fexofenadine but not the excretion of fexofenadine, suggesting that this interaction occurs in the small intestine or in the liver but not in the kidney. A recent jejunal single-pass perfusion study suggested that verapamil treatment did not alter the permeability of fexofenadine.[24] Therefore the interaction between verapamil and fexofenadine might be attributed to the decreased first-pass liver extraction of fexofenadine. Likewise, ketoconazole did not have an impact on the intestinal permeability of fexofenadine.[35]

Verapamil is a nonspecific inhibitor of several membrane transport proteins including P-glycoprotein and OATP-A,[18] whereas several in vitro studies have shown that P-glycoprotein and OATPs have an important role in penetration of the membrane by fexofenadine.[18] Therefore it is most likely that verapamil alters fexofenadine pharmacokinetics through inhibition of P-glycoprotein and OATPs. In comparison with control values, in this study the relative percent of fexofenadine AUC during verapamil coadministration was greater than during probenecid coadministration. Because verapamil has an inhibitory effect on both P-glycoprotein and OATPs, the magnitude of the verapamil-mediated increase in plasma kinetics of fexofenadine might be greater than that of the probenecid-mediated increase.

The renal clearance of fexofenadine was decreased to 27% during probenecid treatment in this study. This finding suggests that fexofenadine excretion in the kidney was inhibited by probenecid probably through OATP inhibition. This is the first report suggesting a specific in vivo contribution of OATPs to fexofenadine excretion. In contrast, only a small, although statistically significant, difference in the plasma kinetics of fexofenadine was found during probenecid treatment. We have 2 plausible explanations for this discrepancy. First, even a pronounced decrease in renal clearance might not have a major impact on fexofenadine dispo-

Table I. Effects of verapamil, cimetidine, and probenecid treatments on pharmacokinetic parameters of fexofenadine after single oral 120-mg dose of fexofenadine in 12 healthy volunteers

Parameter	*Control*	*Verapamil*	*Cimetidine*	*Probenecid*
C_{max} (ng/mL)	611 ± 206	1807 ± 692	609 ± 318	767 ± 490
Ratio to control	1.00	2.92 (2.37-3.95)	0.93 (0.69-1.49)	1.14 (0.85-1.74)
t_{max} (h)	1.5	1.5	2.0	2.0
Median (range)	0.5-4.0	1.0-4.0	1.0-4.0	1.0-4.0
AUC(0-48) (ng · h/mL)	3569 ± 1222	9092 ± 3586	4028 ± 1903	6097 ± 3973
Ratio to control	1.00	2.52 (2.02-3.20)	1.09 (0.79-1.77)	1.54 (1.13-2.46)
AUC(0-∞) (ng · h/mL)	3637 ± 1199	9136 ± 3573	4124 ± 2019	6150 ± 3972
Ratio to control	1.00	2.48 (2.00-3.32)	1.08 (0.77-1.78)	1.53 (1.13-2.40)
Elimination half-life (h)	11.0 ± 5.1	7.9 ± 2.4	9.7 ± 3.1	8.5 ± 1.6
Ratio to control	1.00	0.76 (0.66-0.90)	0.92 (0.80-1.25)	0.84 (0.70-1.13)
Amount excreted (mg)	14.1 ± 4.9	35.5 ± 18.9	10.0 ± 5.1	9.2 ± 11.2
Ratio to control	1.00	2.40 (1.99-3.20)	0.68 (0.52-0.98)	0.43 (0.27-0.97)
CL_{renal} (mL/min)	230 ± 78	224 ± 93	152 ± 70	74 ± 52
Ratio to control	1.00	0.95 (0.77-1.29)	0.61 (0.50-0.98)	0.27 (0.20-0.58)

Data are shown as mean ± SD for pharmacokinetic parameters (except for t_{max}) and geometric mean and 95% confidence interval for ratio to control.
C_{max}, Peak concentration; t_{max}, time to peak concentration in plasma; AUC(0-48), area under plasma concentration–time curve from 0 to 48 hours; AUC(0-∞), area under plasma concentration–time curve from time 0 to infinity; CL_{renal}, renal clearance.

sition because there was only a relatively small amount (about 10%-15%) of fexofenadine excretion in the urine during the control period. Second, it is possible that OATP inhibition by probenecid in the small intestine or liver leads to the decreased bioavailability of fexofenadine. A recent study showed that several fruit juices decreased the plasma concentration of fexofenadine whereas they did not alter renal clearance.[23] Thus the authors of this study concluded that fruit juices decreased oral availability through OATP inhibition in the small intestine.

Probenecid is also an inhibitor of multidrug resistance protein (MRP)–mediated cell efflux.[36] MRP2 is an adenosine triphosphate–binding cassette transporter accepting a diverse range of substrates, including glutathione, glucuronide, and sulfate conjugates of many endobiotics and xenobiotics.[36] MRP2 generally performs excretory or protective roles, and it is expressed on the apical domain of hepatocytes, enterocytes of the proximal small intestine, and proximal renal tubular cells, as well as in the brain and placenta.[36] Thus the significant interaction between fexofenadine and probenecid in this study might be ascribable to MRP inhibition in the liver, small intestine, or kidney, although there is no information indicating the involvement of MRP-mediated cell efflux in fexofenadine disposition. The possibility that several cellular processes other than membrane proteins are involved in this interaction cannot be excluded entirely on the basis of the current data.

It is possible that fexofenadine is a substrate of both OCTs and OATPs because the chemical structure of fexofenadine contains not only a carboxyl group with a negative logarithm of the acid ionization constant (pK_a) equal to 4.25 but also a piperidino group with pK_a equal to 9.53 (Aventis Pharma Co, Tokyo, Japan, personal communication, November 2000), although an in vitro study has suggested that the rat organic cation transporter rOCT1 did not mediate fexofenadine cellar uptake.[18] In this study, however, a relatively small but statistically significant change in urine kinetics was found during coadministration of cimetidine, which is a potent inhibitor of OCT.[27,28,37] In contrast, there was no change in any plasma kinetics of fexofenadine during cimetidine treatment. Therefore it is less likely that fexofenadine disposition is predominantly dependent on changes in OCT activity, suggesting that OCT does not have a major in vivo contribution to fexofenadine disposition.

Verapamil, cimetidine, and probenecid were given before rather than after fexofenadine administration in this study. Because the mean cumulative urinary excretion rate of fexofenadine reached 50% at 4 hours and 89% at 12 hours in comparison with the rate at 48 hours after administration during the control period, urinary excretion was almost complete by 12 hours after fexofenadine administration. Even if these drugs had been continued until the last sampling time point (48 hours), it is unlikely that there would have been significantly

greater differences in plasma and urine kinetics during cimetidine or probenecid treatment.

There was a marked interindividual variation in the pharmacokinetics of fexofenadine in this study (coefficient of variation, 37%-50%; maximum difference, 5.9-fold). This could be explained by large interindividual variation in transporter activity such as P-glycoprotein and OATPs. The MDR1 genotypes T3435C and G2677T/A have a different expression of P-glycoprotein in the small intestine,[38-40] although a previous study failed to find any significant difference in fexofenadine disposition between MDR1 genotypes.[41] Recently, it has been suggested that polymorphisms in OATP-C, such as T521C (Val174Ala), are associated with altered pharmacokinetics of pravastatin.[42] Meanwhile, there is still no evidence of functional polymorphisms in OATP-A, of which fexofenadine is a substrate. Further studies are, therefore, required to explain interindividual variations seen in the pharmacokinetics of fexofenadine, including the contribution of transporters other than OATPs and P-glycoprotein.

A limitation of our study is the 4-way sequence used in the protocol. The control phase was always the first in sequence. Although sufficient washout periods (2 weeks) were used in this study, bias as a result of a sequence effects cannot be excluded.

In conclusion, this study suggests that verapamil increases fexofenadine exposure probably because of an increase in bioavailability through P-glycoprotein inhibition and that probenecid also increases the AUC of fexofenadine, to some extent, as a result of a pronounced reduction in renal clearance. Changes in the regulation of transporters such as P-glycoprotein and OATPs, although not simple, may lead to significant alternation of fexofenadine pharmacokinetics.

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The authors and their institutes have no conflicts of interest.

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